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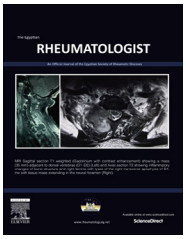

CASE REPORTS

Isolated HBsAg positivity in a Mexican patient with newly diagnosed lupus nephritis

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KEYWORDS

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False positive reactions;
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Abstract *Introduction:* Hepatitis B surface antigen (HBsAg) is usually regarded as a marker of hepatitis B virus (HBV) infection. The concurrence of lupus nephritis (LN) and HBsAg-positivity is a challenge for the clinician, since immunosuppressant use may be associated with an increase in viral replication and an exacerbation of liver disease.

Case presentation: Here, we describe the case of a 30-year-old Mexican woman with newly diagnosed focal proliferative LN who also tested repeatedly positive for HBsAg by chemiluminescent microparticle immunoassay (CMIA). She had no clinical features of hepatitis and her liver function tests were within normal limits. Her abdominal ultrasound was also normal. While waiting for further results, she was started on lamivudine (100 mg daily). However, total HBV core antibody test was negative. Owing to the infrequency of this serological pattern, an in vitro polymerase chain reaction (PCR) assay was performed and HBV was not detected. Overall, we interpreted these results as a false-positive screening. Methylprednisolone pulse therapy was subsequently given (1 g daily for three doses) without hepatic repercussion, neither clinically nor biochemically.

Conclusions: Isolated HBsAg positivity may result from multiple causes, one of which is cross-reactivity. To the best of our knowledge, this is the first report of a false-positive reading using CMIA technique in an active lupus patient. It is reasonable to stress that lupus patients with a positive screening for HBV should undergo a confirmatory assay (such as genomic detection), since this diagnosis may have important therapeutic implications.

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1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder which commonly affects renal function. Its etiology is currently elusive [1]. SLE is characterized by B lymphocyte hyperactivity and autoantibodies against nuclear self-antigens. This condition has a worldwide distribution and predominantly affects women [2]. The prevalence of SLE in the Mexican population has been reported to be 0.6%. Mexican lupus patients tend to have a more severe disease, a lower age of onset than European women and a higher frequency of flares [3,4]. Pregnancy in women with SLE is a significant challenge and the Mexican clinical practice guidelines for the management of such cases integrate the best available evidence for the treatment and follow-up [5].

Hepatitis B and C are among the most important transfusion-transmitted infections and sources of liver diseases worldwide. In Mexico, the prevalence reports of these viruses are scarce and the overall rates were mentioned to be 0.72% (0.63–0.76%) for hepatitis C virus (HCV) and 0.11% (0.08–0.14%) for hepatitis B surface antigen (HBsAg) [6]. The association between chronic HCV infection and SLE may occur. HCV antibodies and active viremia were reported in 20.4% and 8.2% of Egyptian lupus patients, respectively [7]. This frequency differs from one population to another and the prevalence of antibodies against HCV and hepatitis B virus (HBV) in SLE was not higher than in the Mexican general population [8]. Genetic factors play a crucial role in the development of chronic liver disease from HBV infection. In Mexico, there is predominance of genotype H while in Central and South America it is genotype F. Both genotypes appear to be linked to a benign course of disease in contrast to other genotypes in Caucasians that are common in acute and chronic HBV infections. Hepatocellular carcinoma is rare in Mexicans, but it has been associated with genotype F1b among Argentineans [9].

The relationship between SLE and HBV remains incompletely understood. It could be assumed that these patients have a higher prevalence of HBV infection. However, it is comparable with the general population. HBsAg is usually regarded as a marker of HBV infection [1]. Although this is not the case in Mexico, it is not uncommon to find elsewhere patients with lupus nephritis (LN) who also tested positive for HBsAg [8,10]. This concurrence is a challenge for the clinician, since immunosuppressant use may be associated with an increase in viral replication and an exacerbation of liver disease [10].

Here, we describe the case of a young woman with LN who tested repeatedly positive for HBsAg, which was later interpreted as a false-positive reaction, and received methylprednisolone pulse therapy with no hepatic repercussion, neither clinically nor biochemically.

2. Case report

A 30-year-old woman presented to the clinic with 8-months of malaise, alopecia, unexplained weight loss and symmetric polyarthralgia. She also reported one episode of fever three days prior to this visit but denied rashes, photosensitivity, and naso-oral ulcers. She had been taking oral contraceptives for one year, reported having had five sexual partners to date, and inconsistent condom use. She took no regular medication, had not received blood transfusion or vaccination against HBV, and had never been hospitalized before, except for one brief stay for labor and delivery about a year and a half ago, when she was diagnosed with pregnancy-induced hypertension. There were no maternal or fetal complications during this period, and her child is currently healthy, even though she did not breastfeed him.

On physical examination her ankles, wrists and metacarpophalangeal joints were bilaterally tender and swollen. Areas of alopecia were also noted. Laboratory investigation was notable for microcytic anemia (8.7 g/dL) and lymphopenia (658 cells/μL). This evaluation also revealed a serum creatinine of 1.0 mg/dL with blood urea nitrogen of 23 mg/dL, and 1414 mg of proteins in spot urine sample. 20 erythrocytes per high power field (hpf) and 5 leukocytes/hpf were found by urine microscopy. She had hypoalbuminemia (2.3 g/dL) but all other liver function tests (LFTs) were within normal limits (aspartate transaminase 17 IU/L and alanine transaminase 12 IU/L).

She was then admitted for further evaluation and management. The diagnosis of SLE was made briefly after her admission [11] and her SLE disease activity index (SLEDAI-2K) score was 22 [12]. She also met criteria for lupus nephritis [13]. The patient therefore underwent a kidney biopsy, which was consistent with focal proliferative lupus nephritis (Class III [A]) according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) [14], and was started on oral prednisone (30 mg daily), an angiotensin converting enzyme (ACE) inhibitor, hydroxychloroquine (300 mg nightly) and atorvastatin.

The following serological tests were found to be positive in our patient: antinuclear antibodies (1:2560, speckled pattern), anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies (1:1280), and anti-Smith antibodies (77.1 U/mL). She had also hypocomplementemia (C3 37 mg/dL, C4 4.24 mg/dL). Upon her admission, she was offered a screening for HBV (ARCHITECT HBsAg Qualitative II assay, Abbott, Illinois), and she accepted it. Our therapeutic strategy was restrained by this result, since HBsAg test was found to be reactive (2.20 sample/cutoff [S/CO] ratio). She had no clinical features of hepatitis and her LFTs were within normal limits. Abdominal ultrasound was also normal.

While waiting for further results (11 days in total), she was started on lamivudine (100 mg daily). HBV screening was repeated and she tested reactive again (1.85 S/CO). However, total HBV core antibody (anti-HBc) test (ARCHITECT Anti-HBc II assay, Abbott, Illinois) was negative (< 1.00 S/CO). Owing to the infrequency of this serological pattern, an in vitro polymerase chain reaction (PCR) assay (RealTime HBV, Abbott, Illinois) was performed and HBV was not detected. Overall, we interpreted these results as a false-positive screening and, in the following days, methylprednisolone pulse therapy (1 g daily for three doses) was given. This induction had no hepatic repercussion, neither clinically nor biochemically. In conjunction with the patient, we decided to administer intravenous cyclophosphamide in the outpatient setting. However, she did not attend for follow up. During her hospital stay, the patient provided informed consent to report her case.

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3. Discussion

An interplay between SLE and HBV has been formerly pointed out [10]. In our country and abroad, the prevalence of HVB infection is not comparatively higher in lupus patients [8,15]. It has been suggested that, in these patients, their immune response could account for this unexpected prevalence and that IFN-α may have a role in this latter response [15]. The differential diagnosis between LN and HBV-related nephropathy is difficult due to the common clinical features as well as other extrahepatic manifestations [15]. However, in these cases, a correct diagnosis is essential because therapeutic options are quite different.

Although in our patient the diagnostic and therapeutic management was restricted by financial constraint, her clinical picture and paraclinical results lead us to consider that repeatedly positive HBsAg did not actually reflect an HBV infection, but a false-positive reading. We used chemiluminescent microparticle immunoassay (CMIA) as a screening test for HBV infection and, when it tested reactive, we repeated it as suggested by the manufacturer, but at this threshold ratio (S/CO < 100) its positive predictive value is quite limited (27.3%). Therefore, also following the manufacturer's recommendations, a confirmatory test was performed [16]. We did not perform a neutralization assay, but we extended our diagnostic scope by including anti-HBc and PCR. CMIA was also used for determining anti-HBc; this test has a very high specificity (>99%) [17]. Furthermore, the PCR that we used has a specificity of 100% [18]. While waiting for further results, our patient was started on lamivudine because of its rapid and potent antiviral effect [10,19]. This drug has been used in LN patients with HBV infection [10], as well as in those with rapidly progressive glomerulonephritis secondary to HBV [20].

Isolated HBsAg positivity may result from multiple causes. The hypothesis of primary acute infection seems unlikely, considering the PCR detection sensitivity. Anti-HBc negativity is also quite significant since, in these cases, the probability of acute infection in HBsAg positive cases is nil. Our patient had not been previously vaccinated, also ruling out this hypothesis. In our patient, isolated HBsAg positivity could be explained by cross-reactivity [21]. At first glance, our finding (a false-positive HBsAg in a patient with LN) may appear to lack novelty or maybe it could be interpreted as textbook knowledge, something that everyone knows. Nevertheless, this is the first report of a false-positive reading using this technique (CMIA) in an active lupus patient. In previous cases other techniques were used [22], which are no longer in use today. As discussed before, most of weakly positive HBsAg results can be falsely positive [21]. In regions with low prevalence of HBV infection, as in our country [23], most cases of isolated HBsAg positivity can be linked to nonspecific reactivity since true reactivity has not been confirmed by neutralization test or genomic detection [21]. Cross-reactivity has also been described in biopsy tissue of patients with LN, even in those without serological evidence of HBV infection [1].

In conclusion, it is reasonable to stress that lupus patients with a positive screening for HBV should undergo a confirmatory assay (such as genomic detection), since this diagnosis may have important therapeutic implications.

Conflict of interest

None.

References

[1] Wang Z, Li M, Zeng X, Liu X. Hepatitis B virus-associated antigen deposition in renal tissue from patients with systemic lupus erythematosus. J Rheumatol 2012;39:974–8.
[2] Pacheco GV, Novelo Noh IB, Velasco Cárdenas RM, Angulo Ramírez AV, López Villanueva RF, Quintal Ortiz IG, et al. Expression of TLR-7, MyD88, NF-kB, and INF-α in B lymphocytes of Mayan women with systemic lupus erythematosus in Mexico. Front Immunol 2016;7:22.
[3] Peláez-Ballestas I, Sanin L, Moreno-Montoya J, Alvarez-Nemegyei J, Burgos-Vargas R, Garza-Elizondo M, et al. Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. J Rheumatol 2011;38(86):3–8.
[4] Álvarez-Nemegyei J, Peláez-Ballestas I, Sanin L, Cardel M, Ramirez-Angulo A, Goycochea-Robles M. Prevalence of musculoskeletal pain and rheumatic diseases in the southeastern region of Mexico. A COPCORD-based community survey. J Rheumatol Suppl 2011;37(86):21–5.
[5] Saavedra Salinas MÁ, Barrera Cruz A, Cabral Castañeda AR, Jara Quezada LJ, Arce-Salinas CA, Álvarez Nemegyei J, et al. Clinical practice guidelines for the management of pregnancy in women with autoimmune rheumatic diseases of the Mexican College of Rheumatology. Part I. Reumatol Clin 2015;11(5):295–304.
[6] Lopez-Balderas N, Bravo E, Camara M, Hernandez-Romano P. Seroprevalence of hepatitis viruses and risk factors in blood donors of Veracruz, Mexico. J Infect Dev Ctries 2015;9(3):274–82.
[7] El Garf A, Shaheen N, Gaber W, Sobhy N. Prevalence and impact of chronic hepatitis C virus infection on the clinical manifestations and disease activity among patients suffering from systemic lupus erythematosus. Egypt Rheumatol 2013;35(1):9–14.
[8] Mercado U, Avendaño-Reyes M, Araiza-Casillas R, Díaz-Molina R. Prevalence of antibodies against hepatitis C and B in patients with systemic lupus erythematosus. Rev Gastroenterol México 2005;70:399–401.
[9] Roman S, Jose-Abrego A, Fierro NA, Escobedo-Melendez G, Ojeda-Granados C, Martinez-Lopez E, et al. Hepatitis B virus infection in Latin America: a genomic medicine approach. World J Gastroenterol 2014;20(23):7181–96.
[10] Tse K-C, Yung S, Tang C, Yip TP, Chan TM. Management of hepatitis B reactivation in patients with lupus nephritis. Rheumatol Int 2009;29:1273–7.
[11] Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2012;64:2677–86.
[12] Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
[13] Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808.
[14] Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241–50.
[15] Zhao J, Qiu M, Li M, Lu C, Gu J. Low prevalence of hepatitis B virus infection in patients with systemic lupus erythematosus in southern China. Rheumatol Int 2010;30:1565–70.
[16] Sommese L, Iannone C, Cacciatore F, De Iorio G, Napoli C. Comparison between screening and confirmatory serological

assays in blood donors in a Region of South Italy. J Clin Lab Anal 2014;28:198–203.
[17] Seiskari T, Lehtisaari H, Haapala AM, Aittoniemi J. From Abbott ARCHITECT Anti-HBc to Anti-HBc II – improved performance in detecting antibodies to hepatitis B core antigen. J Clin Virol 2010;47:100–1.
[18] Yeh M-L, Huang C-F, Hsieh MY, Huang JF, Dai CY, Yu ML, et al. Comparison of the Abbott RealTime HBV assay with the Roche Cobas AmpliPrep/Cobas TaqMan HBV assay for HBV DNA detection and quantification. J Clin Virol 2014;60:206–14.
[19] Nunes J, Marinho R, Fonseca J, Pereira da Silva JA, Velosa J. Prophylaxis of hepatitis B reactivation with immunosuppressive therapy in rheumatic diseases. Orientations for clinical practice. Acta Reumatol Portuguesa 2011;36:110–8.
[20] Di Marco V, De Lisi S, Li Vecchi M, Maringhini S, Barbaria F. Therapy with lamivudine and steroids in a patient with acute hepatitis B and rapidly progressive glomerulonephritis. Kidney Int 2006;70:1187–8.
[21] Pondé RA. The underlying mechanisms for the isolated positivity for the hepatitis B surface antigen (HBsAg) serological profile. Med Microbiol Immunol 2011;200:13–22.
[22] Celada A, Nydegger UE, Lambert PH, Miescher PA. Hepatitis B antigen and systemic lupus erythematosus. False positive complement fixation due to anti-antibodies. Klin Wochenschr 1976;54:303–7.
[23] Panduro A, Melendez GE, Fierro NA, Madrigal BR, Zepeda-Carrillo EA, Román S. Epidemiology of viral hepatitis in Mexico. Salud Publica Mexico 2011;53:S37–45.

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